Bailey, TG, Perissiou, M, Windsor, M, Schulze, K, Nam, M, Magee, R, Leicht, AS, Green, DJ, Greaves, K, Golledge, J and Askew, CD

Effects of acute exercise on endothelial function in abdominal aortic aneurysm patients.

Articles in PresS. Am J Physiol Heart Circ Physiol (September 22, 2017). doi:10.1152/ajpheart.00344.2017

EFFECTS OF ACUTE EXERCISE ON ENDOTHELIAL FUNCTION IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

TOM G. BAILEY[1]
MARIA PERISSIOU[1]
MARK WINDSOR[1]
KARL SCHULZE[2]
MICHAEL NAM[3]
REBECCA MAGEE[3]
ANTHONY S. LEICHT[4]
DANIEL J. GREEN[5,6]
KIM GREAVES[1,3]
JONATHAN GOLLEDGE[7,8*]
CHRISTOPHER D. ASKEW[1*]

[1] *VasoActive Research Group, School of Health and Sport Sciences,* University of the Sunshine Coast, Maroochydore DC, QLD Australia.
[2]*Sunshine Vascular Clinic*, Buderim, Australia
[3]*Sunshine Coast University Hospital*, Sunshine Coast Hospital and Health Service, Australia
[4] *Sport and Exercise Science,* James Cook University, Townville, Australia
[5]*School of Sport Science, Exercise and Health*, The University of Western Australia
[6]*Research Institute for Sport and Exercise Sciences*, Liverpool John Moores University, UK
[7]*Queensland Research Centre for Peripheral Vascular Disease*, College of Medicine and Dentistry, James Cook University, Townsville, Australia
[8]*Department of Vascular and Endovascular Surgery*, The Townsville Hospital, Townsville, Australia

*Senior authorship responsibilities were shared

SHORT TITLE: Exercise and endothelial function in AAA

AUTHOR FOR CORRESPONDENCE:

A/Prof Christopher Askew, +61 7 5456 5961 caskew@usc.edu.au

ABSTRACT

Endothelial dysfunction is observed in patients with abdominal aortic aneurysm (AAA), who have increased risk of cardiovascular events and mortality. This study aimed to assess the acute effects of moderate and higher-intensity exercise on endothelial function, as assessed by flow-mediated-dilation (FMD), in AAA patients (n=22; 74±6 y) and healthy adults (n=22; 72±5y). Participants undertook three randomised visits, including moderate-intensity continuous exercise (40% peak power output, PPO), higher-intensity interval exercise (70% PPO), and a no-exercise control. Brachial artery FMD was assessed at baseline, 10- and 60-min after each condition. Baseline FMD was lower in AAA patients compared to healthy adults [by 1.10%, (95% CI, 0.72 to 1.81), P=0.044]. There were no group differences in the FMD responses after each condition (P=0.397). FMD did not change after the control condition, but increased by 1.21% (95% CI, 0.69 to 1.73, P<0.001) 10 min after moderate-intensity continuous exercise in both groups, and returned to baseline levels after 60-min. Conversely, FMD decreased by 0.93% (95% CI, 0.41 to 1.44, P<0.001) 10-min after higher-intensity interval exercise in both groups, and remained decreased after 60 min. This study found that the acute response of endothelial function to exercise is intensity-dependent and similar between AAA patients and healthy adults. This provides evidence that regular exercise may improve vascular function in AAA, as it does in healthy adults. Improved FMD following moderate-intensity exercise may provide short-term benefit. Whether the decrease in FMD following higher-intensity exercise represents additional risk and/or a greater stimulus for vascular adaptation remains to be elucidated.

NEW AND NOTEWORTHY

Abdominal aortic aneurysm (AAA) patients have vascular dysfunction. We observed a short-term increase in vascular function after moderate-intensity exercise. Conversely, higher-intensity exercise induced a prolonged reduction in vascular function which may be associated with both short-term increases in cardiovascular risk, and signalling for longer term vascular adaptation in AAA patients.

KEY WORDS

Abdominal aortic aneurysm; exercise; endothelial function; flow-mediated dilation; cardiovascular risk

INTRODUCTION

Abdominal aortic aneurysm (AAA) is characterized by the abnormal progressive dilatation of the abdominal aorta, and is usually diagnosed when maximum abdominal aortic diameter is ≥30 mm (106). Screening studies suggest 1-4% of men and 0.5-1% of women aged over 60 years have an AAA (19, 79). AAA is responsible for ~2% of all deaths (30, 65, 83) and these patients are at high risk of cardiovascular events, such as myocardial infarction and stroke, and mortality compared to age-matched healthy adults (13, 14, 66). These patients also have a risk of aortic rupture due to the weakening of the aortic wall at the site of the aneurysm (25, 63). Currently the only treatment for the weakened aorta is surgical repair, however there is no treatment-related survival benefit in patients with small AAA (<55mm) (27). Screening reduces AAA-related mortality by 50%, yet has no impact on all-cause mortality (29, 105). With AAA there is an increased prevalence of cardiovascular comorbidities, including ischemic heart disease (~45%), myocardial infarction (~27%) and stroke (~14%) (13, 14), and the risk of cardiovascular mortality increases by 3% each year after diagnosis of small AAA (13). Patients with small AAAs are monitored by regular imaging, but up to 70% progress to a diameter ≥55mm necessitating surgical repair (63), with the associated perioperative mortality and morbidity risk (52, 89), and cost. Novel therapies are needed which reduce both the risk of cardiovascular events and the progression of aortic weakening in AAA patients.

Alterations in the connective tissue of the aortic wall, including an imbalance between diminished elastin concentration and collagen proteolysis, is the hallmark of AAA disease. AAA pathogenesis is not well understood, however endothelial dysfunction is suggested to contribute to AAA development via increased oxidative stress, inflammation and impaired NO bioavailability [see recent detailed review (87)]. Thus, treatment that targets endothelial

dysfunction may benefit patients with AAA. Systemic vascular endothelial dysfunction is observed in patients with AAA and has been implicated in AAA growth. For example, reduced bioavailability and sensitivity to nitric-oxide (NO) has been reported in experimental and human AAA (53, 107). Endothelial function, as assessed by flow-mediated dilation (FMD), has been reported to be reduced in patients with AAA compared to healthy adults which is, in part, NO-mediated (35, 58, 112). Importantly, brachial artery FMD is associated with AAA size, future aneurysm growth, and is improved following surgical repair of AAA (58, 61, 93). FMD is also strongly associated with the general risk of cardiovascular-related events and mortality in healthy individuals and those with cardiovascular disease (37, 59). Thus, improving endothelial function could be a valuable treatment target for reducing cardiovascular risk, and possibly limiting aneurysm growth, in patients with AAA.

Brachial FMD improves after regular exercise in patients with known cardiovascular disease and established endothelial dysfunction, including in individuals with coronary and peripheral artery disease (21, 70, 108), suggesting that exercise might be a possible treatment option to reverse endothelial dysfunction in patients with AAA. Vascular improvements with exercise training depend somewhat on the intensity of exercise (76, 84). An important contribution to the beneficial effect of exercise on arterial remodelling has been attributed to the repetitive, acute increases in blood flow and shear stress observed during a single-bout of exercise (36), which have also been suggested to be beneficial for preventing AAA growth at the site of the aorta (3). In healthy adults, endothelial function is reported to increase after low and moderate-intensity exercise, but decrease after higher-intensity exercise (10, 15, 24, 49). The effect of exercise on FMD in individuals with underlying endothelial dysfunction may be augmented (22) compared

to healthy adults (51). However, the effect of exercise intensity on endothelial function in patients with established cardiovascular disease is less clear, with transient increases (23) and decreases (51, 60, 88, 104) in FMD reported after both moderate and higher-intensity exercise. Whether increased exercise intensity has a negative influence at the site of the aneurysm is unclear. However, aortic wall shear stress has been reported to increase during mild and moderate-intensity exercise. and decreases aortic flow stasis associated with aneurysm progression in patients with AAA (91).

To date, exercise therapy in patients with AAA has been prescribed using a relatively low- to moderate-intensity continuous exercise (11, 12, 55, 64, 95, 110). Higher-intensity interval exercise enables a greater volume of exercise to be achieved with shorter bouts, and may have additional cardiovascular benefits in clinical groups, including increases in endothelial function, compared to moderate-intensity continuous exercise (76). Higher-intensity interval exercise has been suggested as an alternative method of training for patients with AAA, but has not been thoroughly investigated (109). A better understanding of the acute effect of different exercise intensities on endothelial function in patients with AAA could provide insight in to the potential role of exercise training in reducing cardiovascular risk and for limiting AAA growth in these individuals. We therefore aimed to determine the effect of a single-bout of moderate- and higher-intensity cycling exercise on FMD in patients with AAA and healthy older adults. We hypothesized that exercise intensity would alter the post-exercise FMD response in both groups, and that the overall FMD response to exercise would be augmented in patients with AAA compared to healthy older adults

METHODS

Participants

All study participants (patients with AAA and healthy adults) were included if they were 60-86 years old, able to exercise and did not have medically untreated, or uncontrolled hypertension (defined as an average SBP ≥140 mmHg and/or an average DBP ≥90 mmHg). For all participants, the exclusion criteria included a BMI over 39, reversible or inducible myocardial ischemia during exercise stress testing for which a cardiologist judged they were not suitable for exercise or diagnosed uncontrolled cardiac arrhythmia with recurrent episodes or symptoms on exertion. Further exclusion included documented medical history of the following; chronic heart failure, severe aortic stenosis, ankylosing spondylitis or chronic obstructive pulmonary disease. Participants with documented peripheral neuropathy, venous insufficiency or any concomitant vascular disease (e.g. Raynaud's or vasculitis) were also excluded prior to study entry. Additional to the above study exclusion criteria, healthy control participants were excluded if they had a family history of AAA or known aneurysmal disease.

Twenty-two males with small AAA (30-45 mm maximal diameter) were recruited from public and private vascular units on the Sunshine Coast, Australia. All patients were under current clinical surveillance and AAA size was confirmed with ultrasound by a trained vascular sonographer at study entry. Twenty-two healthy males were recruited as control participants through local advertisement and from a University of the Sunshine Coast Alumni group. During the study, participants continued to take all prescribed medication. All participants provided written informed consent. The study conformed to the Declaration of Helsinki and was approved

by the human research ethics committees of the Prince Charles Hospital, Brisbane (HREC/12/QPCH/13), and the University of the Sunshine Coast.

Research Design

This was a cross-sectional, randomized cross-over study. AAA and healthy participants underwent four visits on separate days to the clinical exercise physiology laboratory at the University of the Sunshine Coast. Participants refrained from alcohol and exercise for 24h and caffeine for 12h before each visit (97). Visit 1 consisted of measurement of height, body mass, and estimation of body composition using bio-impedance scales (BC 545N, Tanita, Australia). Participants then underwent a maximal incremental cycling test for the determination of VO_{2peak} and peak power output (PPO). Experimental visits (2-4) were conducted in a randomised, counter-balanced order and consisted of two separate acute cycling exercise conditions (moderate-intensity continuous vs. higher-intensity intervals) or a no-exercise control condition (Figure 1). Blood pressure and brachial artery FMD were assessed following 20 min of supine rest at baseline, 10-min and 60-min into recovery after exercise or control conditions. Each experimental visit followed an overnight fast with a standardised breakfast (oat biscuits) 3 hours prior. To control for diurnal variation in blood pressure and vascular function each visit was performed at the same time of day (50). Visits were >3 days apart to ensure recovery between them. All visits were conducted in a mean laboratory temperature of 23 ± 0.9 °C.

Maximal incremental cycling test for determination of cardiorespiratory fitness

After pre-exercise measures, the test commenced with a 3-min warm up at 0W on a cycle ergometer (Lode Corival, Groningen, Netherlands). Intensity then increased to 20W for 1 min,

and by a further 10 W/min until volitional cessation. Participants were required to self-select and maintain a pedal cadence between 60 and 90 RPM throughout the test. Expired gases were continuously collected (Parvo Medics, UT, USA) for the determination of oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$), and the respiratory exchange ratio (RER: $\dot{V}CO_2/\dot{V}O_2$), which were averaged every 15 s. Heart rate was measured continuously using 12-lead ECG (Mortara Inc., WI, USA) and was recorded alongside ratings of perceived effort (RPE) in the final 10 s of each stage. VO_{2peak} was determined as the highest 15s average during the final 60 s of peak exercise. Peak power output (PPO) was used to establish cycling intensity during the subsequent experimental visits.

Experimental exercise and control conditions (visits 2-4)

The experimental protocol is summarised in Figure 1. Following pre-exercise measurements of blood pressure and FMD, participants undertook 27 mins of either: 1) moderate-intensity continuous cycling, 2) higher-intensity interval cycling, or 3) seated-rest as a no-exercise control. Both exercise conditions commenced with a 3-min warm-up at 0W, followed by 24 mins of *i)* moderate-intensity continuous cycling exercise at 40% PPO, or *ii)* higher-intensity interval cycling exercise incorporating 12 x 60 s bouts at 70% PPO, each separated by 60 s at 10% PPO. The moderate-intensity continuous and higher-intensity interval cycling exercise conditions were matched for total duration and work, for each individual. Heart rate (12-lead ECG) and rating of perceived exertion (RPE) (18) were recorded at 60 s intervals throughout each condition. Blood pressure was monitored and recorded every 6-min using a manual sphygmomanometer. During higher-intensity interval exercise, this was performed during the 60s of the high-intensity

intervals. Immediately following each exercise/control condition, participants returned to the supine position for measurement of blood pressure and FMD at 10 and 60 min post.

Measurement of brachial artery FMD

Brachial blood pressure was obtained from the right arm, ≥5 min prior to each brachial artery FMD measurement, and all FMD measurements were performed in line with recent technical recommendations (17, 39, 97). FMD was performed with participants in the supine position, on the right arm with the cuff placed distal to the olecranon process. A 12-MHz multi-frequency linear array probe, attached to a high-resolution duplex ultrasound machine (T3000; Terason, Burlington, MA), was used to image the brachial artery in the distal third of the upper arm to simultaneously record the longitudinal B-mode image and Doppler blood velocity trace. The Doppler angle of insonation was maintained at 60º. Images were optimised, and the settings (depth, focus position and gain) were maintained between FMD assessments within each test visit, as was the location of the probe which was marked on the skin using sweat-resistant ink. Following a 60-s recording period of diameter and velocity, the cuff was rapidly inflated (220 mmHg) and maintained for 5 mins (D.E. Hokanson, Bellevue, WA). Diameter and velocity recordings resumed 30s prior to rapid cuff deflation (<2s) and continued for 3 mins thereafter.

Analysis of brachial artery diameter was performed using custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias. Recent papers contain detailed descriptions of the analysis approach (17, 97). FMD was calculated as [(peak diameter-baseline diameter) / baseline diameter] and expressed as a percent change in vessel diameter. From synchronised diameter and velocity data, blood flow (the product of lumen cross- sectional

area and Doppler velocity) was calculated at 30 Hz. Shear rate was calculated as 4 times mean blood velocity/vessel diameter (expressed as s^{-1}). The coefficient of variation (CV) for baseline FMD% across the three visits in this study was 12.1±2.7 %, which is similar to those previously reported (10.1-14.7%) (101, 111). Using FMD data from our control condition (baseline and 10 min post control) we established that the within-day CV for FMD% was 9.50±4.37 %.

Statistical analysis

Continuous data were normally distributed as assessed by Shapiro-Wilks test. A students *t*-test was used to assess differences in baseline continuous data between patients with AAA and healthy adults. Pearson's Chi Squared test was used to assess differences in categorical data between patients with AAA and healthy adults. A three-way (group*condition*time) linear mixed model (LMM) analysis was used to analyse changes in FMD parameters [brachial diameter, peak diameter and FMD (mm), FMD (%), time to peak, shear rate area-under-the-curve (SRauc), blood flow,] and blood pressure between the two groups (AAA and healthy), across "time" (baseline, 10- and 60-min post) during each condition (control, moderate- and higher-intensity exercise). This LMM analysis allows for random factor subjects and fixed factors of group, condition and time. Absolute FMD (mm) was analysed using a LMM analysis. In line with recent recommendations (9), and to account for the influence of baseline artery diameter on FMD% (5, 7, 8) FMD% was assessed using allometric scaling of logarithmically transformed absolute diameter change (difference between peak artery diameter and baseline diameter in mm). Logarithmically transformed baseline diameter and shear rate were also included as covariates specific to each FMD% test. For each group, condition and time-point, the logged absolute diameter changes were back-transformed and interpreted in the conventional

manner to obtain allometrically scaled FMD (percent diameter change) for comparative purposes in line with recent recommendations (4, 10, 86, 102). All other FMD parameters were not logged for LMM analysis.

To further explore the magnitude and direction of change in FMD% following exercise and control, we used a three-way (group*condition*time) LMM to analyse delta changes from baseline in FMD% (again, with baseline diameter and shear rate specific to each time-point included as covariates). Based on our previous study in healthy older adults (10), we aimed to detect a minimum absolute difference of 1.5% FMD (representing the difference between the change in FMD after moderate and higher-intensity exercise). We required 19 participants per group to detect this difference within and between each group, assuming a 3% standard deviation of the change, and an alpha level of 0.05with a statistical power of 80% (10).

Three-way LMM analysis was also used to detect any differences in heart rate, blood pressure and perceived exertion in response to the acute protocols between the two groups (AAA and healthy adults), across time (at 2 and 6 min intervals for HR/RPE and BP, respectively) during each protocol (control, moderate- and high-intensity exercise). Statistically significant interactions were further investigated with multiple comparisons using the least significant difference approach (71, 82). The strength of the association between AAA diameter, $\dot{V}O_{2peak}$ and FMD% were assessed using Pearson correlation coefficient. Analyses were conducted using the Statistical Package for Social Sciences (Version 22; IBM SPSS Inc., Chicago, IL). Statistical significance was defined at $P<0.05$ and exact P values are cited (P values of "0.000" are reported as "<0.001"). Data are presented in the text as mean (95% confidence interval, 95%CI) unless otherwise stated.

Results

Participant characteristics

Participant characteristics are presented in Table 1. Mean age was similar in AAA and healthy adults (P=0.200). Mean resting blood pressure was similar in patients with AAA and healthy adults. Cardiorespiratory fitness, measured as VO_{2peak}, was significantly lower in patients with AAA compared to healthy adults [mean difference 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (3.4 to 7.3), P<0.001]. Heart rate at peak exercise during the cardiorespiratory fitness test was significantly lower in patients with AAA compared to healthy adults [mean difference of 22 bpm (1 to 31), P<0.001].

Heart rate, blood pressure and perceived exertion during experimental conditions

There were no significant differences between patients with AAA and healthy adults in heart rate, blood pressure and RPE throughout each condition (P>0.05). Heart rate responses during exercise were normalised for the peak heart rate obtained during the cardiorespiratory fitness test in visit 1. Across both groups (*P=0.213*), heart rate was highest during higher-intensity interval exercise [mean 68 $\%HR_{peak}$ (64 to 71 %)] compared to moderate-intensity continuous exercise [mean 62 $\%HR_{peak}$ (59 to 64%, P<0.01)], and lowest during control [mean 42 $\%HR_{peak}$ (95% CI, 39 to 44), P<0.01]. The increase in mean arterial pressure during higher-intensity interval exercise [mean change of 14 mmHg (12 to 17)] was similar during moderate-intensity continuous exercise [mean change of 14 mmHg (11 to 16), P=0.720], whilst increases in mean arterial pressure responses during both exercise conditions were higher compared to control [mean change 10 mmHg (8 to 13), P<0.05]. RPE was higher during higher-intensity interval

304 exercise [mean RPE 4 AU (3 to 4)] compared to during moderate-intensity continuous exercise
305 [mean RPE 3 AU (2 to 3, P <0.001)].
306
307 **Effect of exercise on endothelial function**
308 *Baseline brachial FMD*
309 Brachial FMD was 1.10% (0.72 to 1.81; P=0.044) lower in patients with AAA compared to
310 healthy adults. No differences in baseline brachial artery diameter were observed between groups
311 (P=0.604). SR_{AUC} after cuff deflation was higher in healthy adults compared to patients with
312 AAA [mean difference of 5.7 $10^3 \cdot s^{-1}$ (95% CI, 2.4 to 9.1), P=0.001]. Time to peak diameter was
313 longer in patients with AAA compared to healthy adults [mean difference 14 s (95% CI, 1 to 27),
314 P=0.044]. Baseline FMD and VO_{2peak} were moderately correlated in the combined group of
315 participants (r=0.655, P = 0.006; Figure 2). In patients with AAA, there was a modest, but non-
316 significant inverse correlation between maximum AAA diameter and VO_{2peak} (r=-0.356,
317 P=0.103). There was no significant correlation between maximum AAA diameter and baseline
318 FMD (r=-0.041, P=0.429).
319
320 *FMD responses after exercise and control conditions*
321 Baseline and recovery (10 and 60 min post) brachial FMD% and associated variables are shown
322 in Table 2. The (delta) changes in FMD% from baseline to recovery (10- and 60-min post
323 condition) are shown in Figure 3.
324
325 Brachial FMD increased after moderate-intensity continuous exercise, but decreased after
326 higher-intensity interval exercise in both patients with AAA and healthy adults (Figure 3, Table

2). Overall, there were no differences in the magnitude of the FMD response over time between patients with AAA and the healthy older adults (P=0.154). FMD tended to decrease from baseline after control [at 60-min by 0.43 % (95% CI, -1.10 to 0.96, P=0.115)], but this was not significant. FMD increased from baseline by 1.21% (0.69 to 1.73), P<0.001) at 10-min after moderate-intensity continuous exercise, which then returned to near baseline FMD at 60-min. Conversely, FMD decreased from baseline at 10- and 60-min after higher-intensity interval exercise, by 0.93% (0.41 to 1.44, P<0.001), and 0.51% (0.01 to 1.02, P=0.040)], respectively. Thus, the FMD 10-min after the cessation of exercise was significantly higher after moderate-intensity continuous exercise compared with after control (mean difference in FMD of 1.21 % (95% CI, 0.63 to 1.75, p<0.001) and higher-intensity interval exercise (mean difference of 1.87 % (95% CI, 1.36 to 2.39). At 60-min after exercise, FMD was significantly lower after higher-intensity interval compared to moderate-intensity continuous exercise (mean difference of 0.60 % [95% CI, 0.06 to 1.13], P=0.028). The different responses of FMD% between moderate-intensity continuous and higher-intensity interval exercise were also observed for absolute FMD (mm) (P=0.024; Table 2).

To account for differences in FMD% at baseline between AAA and healthy adults, we calculated the delta change in FMD% after exercise and control (Figure 3). Outcomes of this analysis were consistent with the analysis based on absolute FMD% in Table 2, and we found an intensity*time interaction on delta FMD% (p=0.033), but no differences between groups in the delta FMD % responses after each condition (p=0.522).

Blood flow and shear rate responses after exercise and control

Brachial blood flow and shear rate responses are displayed in Table 2. Resting blood flow was significantly elevated 10 min following both exercise conditions compared to control (P<0.01), and was greater following higher-intensity compared with moderate-intensity exercise [mean difference of 0.38 mL.s^{-1} (95% CI, -0.08 to 0.68), P=0.014] (Table 2). Overall, shear rate was higher in healthy older adults compared to patients with AAA (mean difference of 4.78 s^{-1} (95% CI, 2.21 to 7.35), P=0.002), but was similarly altered by exercise in AAA and healthy adults (P=0.760). Shear rate was elevated 10 min after both exercise protocols compared with control (Table 2, P=0.005), and was similar after higher-intensity interval compared to moderate-intensity continuous exercise [mean difference of 1.14 10^{3} s^{-1} (95% CI, -1.22 to 3.16), P=0.342].

Heart rate and blood pressure responses after exercise

There was a condition*time interaction for HR, SBP and MAP (P<0.001, see Table 2) where the mean changes in HR (increase), SBP and MAP (decrease) were larger after exercise compared to those observed after control. Moreover, no group differences were observed for the HR (P=0.885) and blood pressure (P=0.553) responses following each condition. Overall, MAP decreased by 3 mmHg (95% CI, 1 to 5, P<0.004) and 4 mmHg (95% CI, 2 to 6, P<0.001) 60-min after moderate- and high-intensity exercise, respectively, compared to control.

Discussion

To our knowledge, this is the first study to assess the response of endothelial function during early recovery from different exercise intensities in patients with AAA. The main finding of this study was that the response of FMD to a single bout of cycling exercise was similar in patients with AAA compared to healthy adults of the same age and sex. For both groups, we observed an

immediate increase in FMD following moderate-intensity continuous exercise, which returned to near-baseline levels after one hour of recovery. In contrast, FMD decreased immediately following higher-intensity interval exercise and remained decreased after one hour in both groups.

Basal FMD in patients with AAA

In this study, we observed reduced basal FMD in patients with AAA compared to healthy adults, which is consistent with previous reports (61, 94). Previous studies assessing FMD in AAA fail to report cardiorespiratory fitness levels, which may also contribute to differences in FMD%. Poor fitness has previously been shown to be associated with impaired FMD (62), and we observed a significant relationship between resting FMD and $\dot{V}O_{2peak}$ in this study.

Impaired FMD is independently associated with an increased risk of cardiovascular events and mortality (37, 48, 54, 92), and may contribute to the high burden of cardiovascular disease and the observation that ~70% of cardiovascular events and mortality in patients that have small AAAs is independent of aneurysm-related complications (57, 66, 72). As expected, there was a higher prevalence of comorbidities amongst the patients with AAA compared to the healthy adults, such as hypertension and dyslipidaemia, which may have contributed to the impairment of endothelial function identified (26, 96). Patients with AAA also have a higher prevalence of comorbidities compared to other surgical populations including cardiac (60-70%), respiratory (50%), and kidney and metabolic disease (10-12%) , all of which are associated with vascular dysfunction (28, 44, 68, 77). Poor endothelial function in patients with AAA might contribute to

their elevated cardiovascular risk, and is likely to be exacerbated by the presence of comorbidities, which reinforces the potential of FMD as a treatment target for this population.

Time course of FMD response to exercise

The increase in FMD after moderate-intensity exercise in this study has been observed in some (10, 20, 49, 80), but not all (22, 114) previous studies of healthy adults and those with cardiovascular disease. Similarly, the observed decrease in FMD after higher-intensity exercise has been reported in some (15, 51), but not all (23) studies. Discrepancies between studies may be related to the timing of measurements after exercise as the FMD response to acute exercise is suggested to be bi-phasic, with an immediate decrease followed by an increase or return to baseline FMD after a further period of recovery (1-24h) (24). In this study, we attempted to capture the bi-phasic response by measuring FMD immediately, and then one hour after exercise. We found an immediate increase in FMD that then returned to baseline one hour after moderate-intensity continuous exercise, but an immediate and prolonged decrease in FMD after higher-intensity interval exercise. These responses are in line with our previous findings in older adults that have a poor cardiorespiratory fitness (10), and in patients with peripheral arterial disease (51). It is possible that we may have observed an improvement in FMD with an extended recovery period after the higher-intensity exercise, as other studies in individuals with established endothelial dysfunction have demonstrated a delayed increase in FMD 1-4 hours after exercise (20, 40).

Our findings of no difference in the FMD response after exercise between AAA and healthy adults in this study were somewhat unexpected. It has previously been suggested that a

418 "basement effect" exists in older adults with poor endothelial function, where there is an
419 incapacity for a decrease in FMD after exercise (78). In patients with coronary artery disease
420 who exhibit severe endothelial dysfunction an increase, not a decrease, was observed in FMD
421 after exercise, yet no direct comparisons were made to healthy adults of similar age (22). In this
422 study, both the patients with AAA and the healthy older adults exhibited a degree of endothelial
423 dysfunction at rest compared with values reported in healthy younger adults (16), potentially due
424 to older age (99). Despite differences in fitness between groups in this study and its relationship
425 with endothelial function, the fitness of both groups was "poor" based on normative values for
426 healthy older adults (1). Further, despite observing no differences in the FMD response between
427 normotensive and controlled hypertensive individuals in this study (data not shown), we cannot
428 rule out the potential confounding influence of other known comorbidities and antihypertensive-,
429 statin- and β-blocker medication on the FMD responses. Nonetheless, cardiovascular risk factors
430 such as hypertension and known cardiovascular disease, including coronary heart disease, stroke
431 and previous myocardial infarction are highly prevalent in patients with small AAA (13, 14) and
432 as such our findings are likely to be generalizable to this patient group. Including a comparative
433 group with known cardiovascular risk factors and disease may allow for the influence of AAA to
434 be separated from the influence of other cardiovascular comorbidities. The similar responses in
435 FMD after exercise in both groups in this study suggests the exercise stimulus *per se* affects the
436 endothelium in older-aged individuals in a similar way, irrespective of the resting level of
437 endothelial function, disease status, medication use or known cardiovascular risk factors.
438
439 Shear rate was lower throughout all conditions and time-points in patients with AAA compared
440 with healthy older adults. Shear stress is proposed as the primary stimulus for FMD (75, 97), and

may therefore have contributed to the lower FMD in patients with AAA. Whilst simple normalization of FMD to shear rate is sometimes utilised (74), we found no linear relationship between FMD and shear rate (P=0.271, r= 0.21), and therefore used a recommended statistical model that controlled for shear rate and baseline diameter (6, 9). Given we observed no group differences in brachial artery diameter, the lower shear rate is likely a consequence of the decreased reactive hyperaemia in patients with AAA in this study, which may be indicative of microvascular impairment. As peak reactive hyperaemia is also predictive of future cardiovascular events in vascular patients (45), further studies investigating microvascular function in patient with AAA are warranted.

As we did not directly assess all the mechanisms responsible for exercise-intensity dependent changes in FMD, we can only speculate on the possible causes, which are suggested to include changes in blood pressure, shear stress, reactive oxygen species and sympathetic nervous activity (24). Blood pressure did not differ significantly during and after moderate- and higher-intensity exercise, and is therefore unlikely to explain the observed differences in FMD responses. NO bioavailability has been shown to be impaired in patients with AAA (53, 87), and therefore altered NO bioavailability after moderate-intensity exercise may explain the increase in FMD. Blood flow patterns during exercise, including increased antegrade flow and shear stress, enhances NO availability and increases FMD (98, 101, 103). Conversely increases in exercise intensity and oscillatory shear and/or retrograde flow increase reactive oxygen species, including superoxide anions (32, 47), which are capable of scavenging NO. This is suggested to reduce FMD in atherosclerotic-prone arteries (85), which may include and be acutely detrimental to the aorta, however this is unknown. The observed decrease in brachial FMD following higher-

intensity interval-based exercise in this study may be attributed to repeated and abrupt increases in brachial artery oscillatory flow (101) observed at the onset of cycling exercise (34), whereas continuous rhythmic exercise elevates antegrade blood flow and increases FMD (100, 103). There is also evidence to suggest that FMD may not be solely NO-mediated (69, 73, 112), and hence other factors should also be considered. Reductions in FMD after higher-intensity, but not moderate-intensity exercise, may be due to a dose-dependent increase in oxidative stress (32), endothelin-1 expression (42), or increased sympathetic nervous activity (41), that negatively impacts endothelial function.

If the changes in brachial artery FMD responses to exercise mirror changes in the aorta, it is possible that different exercise intensities may have differing effects on aortic remodelling, and potentially AAA growth and rupture risk. This, however, remains to be investigated. Interestingly, aortic blood flow increases during steady-state moderate-intensity cycling exercise in patients with AAA, enhances wall shear stress and decreases platelet aggregation which has been suggested to be conducive to preventing AAA progression (43). Whether this proposed benefit remains during higher-intensity interval exercise warrants investigation, although exercise-induced increases in shear stress may enhance eNOS expression and vascular repair mechanisms (81), including the mobilisation of endothelial progenitor cells (113). We did not measure the effect of exercise on aortic endothelial function in this study, however it has recently been reported that brachial artery FMD is improved following surgical repair of AAA (58), suggesting a direct association between aortic and systemic endothelial health in patients with AAA.

FMD responses and potential adaptations with exercise training

The rationale for assessing the time-course of responses in endothelial function after a single bout of exercise relates to the potential impact of repeated bouts on vascular adaptation with exercise training (38). FMD is improved following exercise training in sedentary elderly individuals (56), and the similar acute FMD responses between patients with AAA and healthy adults in this study suggest a capacity for vascular adaptation in AAA patients. Importantly, FMD may be further improved after higher-intensity compared to moderate-intensity exercise training in older adults and in individuals with cardiovascular disease (33, 76, 84). Whether the difference in the acute FMD responses between moderate- and higher-intensity exercise is important for future vascular adaptation in patients with AAA is currently unknown. A reduction in FMD for 60 minutes after higher-intensity interval exercise observed in this study may be linked to vascular remodelling after a period of exercise training (67). Myers et al (2014) reported no significant effect on AAA size after a two year exercise therapy intervention, despite a tendency for a slower aneurysm growth rate after exercise training compared to usual care (64). That study only used low-to-moderate intensity exercise, and this raises the possibility that any potential benefit of exercise on vascular function and AAA growth may be dependent on higher-intensity exercise that promotes a greater perturbation in arterial haemodynamics and endothelial function.

Exercise and CV risk in patients with AAA

While the absolute risk of exercise is low, acute cardiovascular events induced by a single-bout of exercise are more common in the elderly and those with atherosclerotic disease (2). Exercise studies in patients with AAA to date have adopted a conservative approach, potentially due to

concerns over the safety of higher-intensity exercise in patients deemed high-risk. Higher intensity interval exercise is increasingly being prescribed for patients with cardiovascular disease and other chronic conditions (21, 46, 76, 84, 90, 114), and our study is the first to report the short-term vascular effects of higher-intensity exercise in patients with AAA. Long-term, a decrease in FMD of 1% has been associated with a 9-17% increase in cardiovascular event rate (37, 48). Whether the acute decreases in FMD (of ~1.0% after higher-intensity interval exercise in this study) are associated with increased risk of acute events, or conversely are important in triggering the benefits of exercise, is not known (31, 67). The use of higher-intensity exercise in patients with AAA needs to consider the short-term, potentially harmful, reduction in endothelial function and the possible benefits of improved cardiorespiratory fitness and endothelial function in the longer term. A recent hospital-based study using high-intensity exercise in patients with AAA reported no detrimental effects, although measures of cardiovascular function were not reported (109).

This study has some limitations that should be noted. Since AAA is asymptomatic it is possible that some of the healthy controls could have had an AAA, although given the low prevalence of AAA, this is unlikely. We only recruited men and therefore the findings may not be generalised to women with AAA. We cannot rule out the potential influence of cardiovascular risk reducing medication on the current findings, including antihypertensive and statin therapy, and further research is needed to understand the direct impact of medication use on the FMD response to exercise in patients with cardiovascular disease. Nonetheless, this is the first study to investigate the acute effects of different exercise-intensities on endothelial function in patients with AAA compared to healthy adults. Further studies are required to more fully explore the interaction

between exercise intensity, endothelial function and cardiovascular risk in patients with AAA. Investigations of the longer-term benefits of higher-intensity exercise training in patients with an AAA are warranted.

Conclusions

The present study suggests that the acute FMD responses to exercise in patients with AAA are similar to healthy adults of similar age. We show that FMD transiently improves after moderate-intensity continuous exercise whereas decreases in FMD are observed for up to one hour after higher-intensity interval exercise. Future studies on the effects of exercise training will be important to better understand the role of transient changes in endothelial function with acute exercise on AAA growth and cardiovascular risk.

CONFLICT OF INTEREST: NONE

FUNDING: This research was funded by grants from the National Health and Medical Research Council (1000967, 1022752, 1079369), The Townsville Hospital, and the Inflammation and Healing Cluster at the University of the Sunshine Coast. Professor Green's research is supported by an NHMRC Principal Research Fellowship (1090914). Professor Jonathan Golledge's work is supported by fellowships from the NHMRC (1117061) and the Queensland Government (Senior Clinical Research Fellowship).

References

1. **ACSM**. *ACSM's Guidelines for Exercise Testing and Prescription*. Baltimore, USA: 2014.
2. **Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, and Manson JE**. Triggering of sudden death from cardiac causes by vigorous exertion. *The New England journal of medicine* 343: 1355-1361, 2000.
3. **Arzani A, Les AS, Dalman RL, and Shadden SC**. Effect of exercise on patient specific abdominal aortic aneurysm flow topology and mixing. *International journal for numerical methods in biomedical engineering* 30: 280-295, 2014.
4. **Atkinson CL, Carter HH, Dawson EA, Naylor LH, Thijssen DH, and Green DJ**. Impact of handgrip exercise intensity on brachial artery flow-mediated dilation. *Eur J Appl Physiol* 115: 1705-1713, 2015.
5. **Atkinson G**. The dependence of FMD% on baseline diameter: a problem solved by allometric scaling. *Clinical science (London, England : 1979)* 125: 53-54, 2013.
6. **Atkinson G**. Shear rate normalization is not essential for removing the dependency of flow-mediated dilation on baseline artery diameter: past research revisited. *Physiological Measurement* 35: 1825-1835, 2014.
7. **Atkinson G, and Batterham AM**. Allometric scaling of diameter change in the original flow-mediated dilation protocol. *Atherosclerosis* 226: 425-427, 2013.
8. **Atkinson G, and Batterham AM**. The clinical relevance of the percentage flow-mediated dilation index. *Curr Hypertens Rep* 17: 4, 2015.
9. **Atkinson G, Batterham AM, Thijssen DH, and Green DJ**. A new approach to improve the specificity of flow-mediated dilation for indicating endothelial function in cardiovascular research. *Journal of hypertension* 31: 287-291, 2013.
10. **Bailey TG, Perissiou M, Windsor M, Russell F, Golledge J, Green DJ, and Askew CD**. Cardiorespiratory fitness modulates the acute flow-mediated dilation response following high-intensity but not moderate-intensity exercise in elderly men. *Journal of applied physiology (Bethesda, Md : 1985)* 122: 1238-1248, 2017.
11. **Barakat HM, Shahin Y, Barnes R, Gohil R, Souroullas P, Khan J, McCollum PT, and Chetter IC**. Supervised exercise program improves aerobic fitness in patients awaiting abdominal aortic aneurysm repair. *Annals of vascular surgery* 28: 74-79, 2014.
12. **Barakat HM, Shahin Y, Khan JA, McCollum PT, and Chetter IC**. Preoperative Supervised Exercise Improves Outcomes After Elective Abdominal Aortic Aneurysm Repair: A Randomized Controlled Trial. *Annals of surgery* 264: 47-53, 2016.
13. **Bath MF, Gokani VJ, Sidloff DA, Jones LR, Choke E, Sayers RD, and Bown MJ**. Systematic review of cardiovascular disease and cardiovascular death in patients with a small abdominal aortic aneurysm. *The British journal of surgery* 102: 866-872, 2015.
14. **Bath MF, Saratzis A, Saedon M, Sidloff D, Sayers R, and Bown MJ**. Patients with Small Abdominal Aortic Aneurysm are at Significant Risk of Cardiovascular Events and this Risk is not Addressed Sufficiently. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 53: 255-260, 2017.
15. **Birk GK, Dawson EA, Batterham AM, Atkinson G, Cable T, Thijssen DH, and Green DJ**. Effects of exercise intensity on flow mediated dilation in healthy humans. *Int J Sports Med* 34: 409-414, 2013.

16. **Black MA, Cable NT, Thijssen DH, and Green DJ**. Impact of age, sex, and exercise on brachial artery flow-mediated dilatation. *American journal of physiology Heart and circulatory physiology* 297: H1109-1116, 2009.
17. **Black MA, Cable NT, Thijssen DH, and Green DJ**. Importance of measuring the time course of flow-mediated dilatation in humans. *Hypertension* 51: 203-210, 2008.
18. **Borg G**. [Physical training. 3. Perceived exertion in physical work]. *Lakartidningen* 67: 4548-4557, 1970.
19. **Cornuz J, Sidoti Pinto C, Tevaearai H, and Egger M**. Risk factors for asymptomatic abdominal aortic aneurysm: systematic review and meta-analysis of population-based screening studies. *European journal of public health* 14: 343-349, 2004.
20. **Cosio-Lima LM, Thompson PD, Reynolds KL, Headley SA, Winter CR, Manos T, Lagasse MA, Todorovich JR, and Germain M**. The acute effect of aerobic exercise on brachial artery endothelial function in renal transplant recipients. *Prev Cardiol* 9: 211-214, 2006.
21. **Currie KD, Dubberley JB, McKelvie RS, and MacDonald MJ**. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc* 45: 1436-1442, 2013.
22. **Currie KD, McKelvie RS, and Macdonald MJ**. Brachial artery endothelial responses during early recovery from an exercise bout in patients with coronary artery disease. *BioMed research international* 2014: 591918, 2014.
23. **Currie KD, McKelvie RS, and Macdonald MJ**. Flow-mediated dilation is acutely improved after high-intensity interval exercise. *Med Sci Sports Exerc* 44: 2057-2064, 2012.
24. **Dawson EA, Green DJ, Cable NT, and Thijssen DH**. Effects of acute exercise on flow-mediated dilatation in healthy humans. *Journal of applied physiology (Bethesda, Md : 1985)* 115: 1589-1598, 2013.
25. **Emeto TI, Seto SW, and Golledge J**. Targets for medical therapy to limit abdominal aortic aneurysm progression. *Current drug targets* 15: 860-873, 2014.
26. **ESVS**. Second Vascular Surgery Database Report 2008.
27. **Filardo G, Powell JT, Martinez MA, and Ballard DJ**. Surgery for small asymptomatic abdominal aortic aneurysms. *The Cochrane database of systematic reviews* Cd001835, 2015.
28. **Gander JC, Sui X, Hebert JR, Hazlett LJ, Cai B, Lavie CJ, and Blair SN**. Association of Cardiorespiratory Fitness With Coronary Heart Disease in Asymptomatic Men. *Mayo Clin Proc* 90: 1372-1379, 2015.
29. **Glover MJ, Kim LG, Sweeting MJ, Thompson SG, and Buxton MJ**. Cost-effectiveness of the National Health Service abdominal aortic aneurysm screening programme in England. *British Journal of Surgery* 101: 976-982, 2014.
30. **Golledge J, Muller J, Daugherty A, and Norman P**. Abdominal Aortic Aneurysm: Pathogenesis and Implications for Management. *Arterioscler Thromb Vasc Biol* 26: 2605-2613, 2006.
31. **Goodman JM, Burr JF, Banks L, and Thomas SG**. The Acute Risks of Exercise in Apparently Healthy Adults and Relevance for Prevention of Cardiovascular Events. *The Canadian journal of cardiology* 32: 523-532, 2016.
32. **Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, Kawamura M, Chayama K, Yoshizumi M, and Nara I**. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation* 108: 530-535, 2003.
33. **Grace FM, Herbert P, Ratcliffe JW, New KJ, Baker JS, and Sculthorpe NF**. Age related vascular endothelial function following lifelong sedentariness: positive impact of

cardiovascular conditioning without further improvement following low frequency high intensity interval training. *Physiological reports* 3: 2015.

34. **Green DJ, Bilsborough W, Naylor LH, Reed C, Wright J, O'Driscoll G, and Walsh JH**. Comparison of forearm blood flow responses to incremental handgrip and cycle ergometer exercise: relative contribution of nitric oxide. *J Physiol* 562: 617-628, 2005.

35. **Green DJ, Dawson EA, Groenewoud HM, Jones H, and Thijssen DH**. Is flow-mediated dilation nitric oxide mediated?: A meta-analysis. *Hypertension* 63: 376-382, 2014.

36. **Green DJ, Hopman MTE, Padilla J, Laughlin MH, and Thijssen DHJ**. Vascular adaptation to exercise in humans: The role of hemodynamic stimuli. *Physiological reviews* In Press Sept 13.: 2016.

37. **Green DJ, Jones H, Thijssen D, Cable NT, and Atkinson G**. Flow-mediated dilation and cardiovascular event prediction. *Hypertension* 57: 363-369, 2011.

38. **Green DJ, Maiorana A, O'Driscoll G, and Taylor R**. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol* 561: 1-25, 2004.

39. **Harris RA, Nishiyama SK, Wray DW, and Richardson RS**. Ultrasound assessment of flow-mediated dilation. *Hypertension* 55: 1075-1085, 2010.

40. **Harris RA, Padilla J, Hanlon KP, Rink LD, and Wallace JP**. The Flow-mediated Dilation Response to Acute Exercise in Overweight Active and Inactive Men. *Obesity* 16: 578-584, 2008.

41. **Hijmering ML, Stroes ES, Olijhoek J, Hutten BA, Blankestijn PJ, and Rabelink TJ**. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 39: 683-688, 2002.

42. **Himburg HA, Dowd SE, and Friedman MH**. Frequency-dependent response of the vascular endothelium to pulsatile shear stress. *American journal of physiology Heart and circulatory physiology* 293: H645-653, 2007.

43. **Hoshina K, Sho E, Sho M, Nakahashi TK, and Dalman RL**. Wall shear stress and strain modulate experimental aneurysm cellularity. *Journal of vascular surgery* 37: 1067-1074, 2003.

44. **Howden EJ, Weston K, Leano R, Sharman JE, Marwick TH, Isbel NM, and Coombes JS**. Cardiorespiratory fitness and cardiovascular burden in chronic kidney disease. *Journal of science and medicine in sport / Sports Medicine Australia* 18: 492-497, 2015.

45. **Huang AL, Silver AE, Shvenke E, Schopfer DW, Jahangir E, Titas MA, Shpilman A, Menzoian JO, Watkins MT, Raffetto JD, Gibbons G, Woodson J, Shaw PM, Dhadly M, Eberhardt RT, Keaney JF, Gokce N, and Vita JA**. Predictive Value of Reactive Hyperemia for Cardiovascular Events in Patients With Peripheral Arterial Disease Undergoing Vascular Surgery. *Arterioscler Thromb Vasc Biol* 27: 2113-2119, 2007.

46. **Hwang C-L, Yoo J-K, Kim H-K, Hwang M-H, Handberg EM, Petersen JW, and Christou DD**. Novel all-extremity high-intensity interval training improves aerobic fitness, cardiac function and insulin resistance in healthy older adults. *Experimental gerontology* 82: 112-119, 2016.

47. **Hwang J, Ing MH, Salazar A, Lassegue B, Griendling K, Navab M, Sevanian A, and Hsiai TK**. Pulsatile versus oscillatory shear stress regulates NADPH oxidase subunit expression: implication for native LDL oxidation. *Circulation research* 93: 1225-1232, 2003.

48. **Inaba Y, Chen J, and Bergmann S**. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging)* 26: 631-640, 2010.

692 49. **Johnson BD, Padilla J, and Wallace JP**. The exercise dose affects oxidative stress and
693 brachial artery flow-mediated dilation in trained men. *Eur J Appl Physiol* 112: 33-42, 2012.
694 50. **Jones H, Green DJ, George K, and Atkinson G**. Intermittent exercise abolishes the
695 diurnal variation in endothelial-dependent flow-mediated dilation in humans. *American journal*
696 *of physiology Regulatory, integrative and comparative physiology* 298: R427-432, 2010.
697 51. **Joras M, and Poredos P**. The association of acute exercise-induced ischaemia with
698 systemic vasodilator function in patients with peripheral arterial disease. *Vascular medicine*
699 *(London, England)* 13: 255-262, 2008.
700 52. **Karthikesalingam A, Holt PJ, Vidal-Diez A, Bahia SS, Patterson BO, Hinchliffe RJ,**
701 **and Thompson MM**. The impact of endovascular aneurysm repair on mortality for elective
702 abdominal aortic aneurysm repair in England and the United States. *Journal of vascular surgery*
703 2016.
704 53. **Knipp BS, Peterson DA, Rajagopalan S, Kehrer C, Ford JW, D'Alecy LG, Whitesall**
705 **SE, Eagleton MJ, Wakefield TW, Henke PK, Jacobs LA, Greenfield LJ, Stanley JC, and**
706 **Upchurch GR, Jr.** Impaired vasoreactivity despite an increase in plasma nitrite in patients with
707 abdominal aortic aneurysms. *Journal of vascular surgery* 35: 363-367, 2002.
708 54. **Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka**
709 **K, Shimano H, Ohashi Y, Yamada N, and Sone H**. Cardiorespiratory fitness as a quantitative
710 predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-
711 analysis. *JAMA : the journal of the American Medical Association* 301: 2024-2035, 2009.
712 55. **Kothmann E, Batterham AM, Owen SJ, Turley AJ, Cheesman M, Parry A, and**
713 **Danjoux G**. Effect of short-term exercise training on aerobic fitness in patients with abdominal
714 aortic aneurysms: a pilot study. *British journal of anaesthesia* 103: 505-510, 2009.
715 56. **Landers-Ramos RQ, Corrigan KJ, Guth LM, Altom CN, Spangenburg EE, Prior**
716 **SJ, and Hagberg JM**. Short-term exercise training improves flow-mediated dilation and
717 circulating angiogenic cell number in older sedentary adults. *Applied physiology, nutrition, and*
718 *metabolism = Physiologie appliquee, nutrition et metabolisme* 41: 832-841, 2016.
719 57. **Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, Ballard**
720 **DJ, Messina LM, Gordon IL, Chute EP, Krupski WC, Busuttil SJ, Barone GW, Sparks S,**
721 **Graham LM, Rapp JH, Makaroun MS, Moneta GL, Cambria RA, Makhoul RG, Eton D,**
722 **Ansel HJ, Freischlag JA, and Bandyk D**. Immediate repair compared with surveillance of
723 small abdominal aortic aneurysms. *The New England journal of medicine* 346: 1437-1444, 2002.
724 58. **Lee R, Bellamkonda K, Jones A, Killough N, Woodgate F, Williams M, Cassimjee I,**
725 **and Handa A**. Flow Mediated Dilatation and Progression of Abdominal Aortic Aneurysms.
726 *European journal of vascular and endovascular surgery : the official journal of the European*
727 *Society for Vascular Surgery* 53: 820-829, 2017.
728 59. **Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, and Lerman A**. Prognostic Value
729 of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular
730 Events: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association* 4:
731 2015.
732 60. **McGowan CL, Levy AS, Millar PJ, Guzman JC, Morillo CA, McCartney N, and**
733 **Macdonald MJ**. Acute vascular responses to isometric handgrip exercise and effects of training
734 in persons medicated for hypertension. *American journal of physiology Heart and circulatory*
735 *physiology* 291: H1797-1802, 2006.

61. **Medina F, de Haro J, Florez A, and Acin F**. Relationship between endothelial dependent vasodilation and size of abdominal aortic aneurysms. *Annals of vascular surgery* 24: 752-757, 2010.
62. **Montero D**. The association of cardiorespiratory fitness with endothelial or smooth muscle vasodilator function. *European journal of preventive cardiology* 22: 1200-1211, 2015.
63. **Moxon JV, Parr A, Emeto TI, Walker P, Norman PE, and Golledge J**. Diagnosis and monitoring of abdominal aortic aneurysm: current status and future prospects. *Curr Probl Cardiol* 35: 512-548, 2010.
64. **Myers J, McElrath M, Jaffe A, Smith K, Fonda H, Vu A, Hill B, and Dalman R**. A randomized trial of exercise training in abdominal aortic aneurysm disease. *Med Sci Sports Exerc* 46: 2-9, 2014.
65. **Nordon IM, Hinchliffe RJ, Loftus IM, and Thompson MM**. Pathophysiology and epidemiology of abdominal aortic aneurysms. *Nature reviews Cardiology* 8: 92-102, 2011.
66. **Ouriel K, Clair DG, Kent KC, and Zarins CK**. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. *Journal of vascular surgery* 51: 1081-1087, 2010.
67. **Padilla J, Simmons GH, Bender SB, Arce-Esquivel AA, Whyte JJ, and Laughlin MH**. Vascular effects of exercise: Endothelial adaptations beyond active muscle beds. *Physiology* 26: 132-145, 2011.
68. **Pandey A, Garg S, Khunger M, Garg S, Kumbhani DJ, Chin KM, and Berry JD**. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circulation Heart failure* 8: 1032-1043, 2015.
69. **Parker BA, Tschakovsky ME, Augeri AL, Polk DM, Thompson PD, and Kiernan FJ**. Heterogenous vasodilator pathways underlie flow-mediated dilation in men and women. *American journal of physiology Heart and circulatory physiology* 301: H1118-1126, 2011.
70. **Pearson MJ, and Smart NA**. Effect of exercise training on endothelial function in heart failure patients: A systematic review meta-analysis. *International journal of cardiology* 231: 234-243, 2017.
71. **Perneger TV**. Whats wrong with Bonferroni adjustments? *British Medical Journal* 316: 1236, 1998.
72. **Pretre R, and Turina M**. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 352: 1649-1655, 1998.
73. **Pyke K, Green DJ, Weisbrod C, Best M, Dembo L, O'Driscoll G, and Tschakovsky M**. Nitric oxide is not obligatory for radial artery flow-mediated dilation following release of 5 or 10 min distal occlusion. *American journal of physiology Heart and circulatory physiology* 298: H119-126, 2010.
74. **Pyke KE, Dwyer EM, and Tschakovsky ME**. Impact of controlling shear rate on flow-mediated dilation responses in the brachial artery of humans. *Journal of applied physiology (Bethesda, Md : 1985)* 97: 499-508, 2004.
75. **Pyke KE, and Tschakovsky ME**. The relationship between shear stress and flow-mediated dilatation: implications for the assessment of endothelial function. *J Physiol* 568: 357-369, 2005.
76. **Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, and Coombes JS**. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular

function: a systematic review and meta-analysis. *Sports medicine (Auckland, NZ)* 45: 679-692, 2015.

77. **Ramos JS, Ramos MV, Dalleck LC, Borrani F, Walker KB, Fassett RG, Sharman JE, and Coombes JS**. Fitness Is Independently Associated with Central Hemodynamics in Metabolic Syndrome. *Medicine & Science in Sports & Exercise* 48: 1539-1547, 2016.

78. **Ranadive SM, Kappus RM, Cook MD, Yan H, Lane AD, Woods JA, Wilund KR, Iwamoto G, Vanar V, Tandon R, and Fernhall B**. Effect of acute moderate exercise on induced inflammation and arterial function in older adults. *Experimental Physiology* 99: 729-739, 2014.

79. **Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Halperin JL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, and Zierler RE**. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline). *Vascular medicine (London, England)* 16: 452-476, 2011.

80. **Rooks CR, McCully KK, and Dishman RK**. Acute exercise improves endothelial function despite increasing vascular resistance during stress in smokers and nonsmokers. *Psychophysiology* 48: 1299-1308, 2011.

81. **Ross MD, Malone E, and Florida-James G**. Vascular Ageing and Exercise: Focus on Cellular Reparative Processes. *Oxid Med Cell Longev* 2016: 3583956, 2016.

82. **Rothman KJ**. No adjustments are needed for multiple comparisons. *Epidemiology* 1: 43-46, 1990.

83. **Sampson UKA, Norman PE, Fowkes FGR, Aboyans V, Song Y, Harrell Jr FE, Forouzanfar MH, Naghavi M, Denenberg JO, McDermott MM, Criqui MH, Mensah GA, Ezzati M, and Murray C**. Global and regional burden of aortic dissection and aneurysms: Mortality trends in 21 world regions, 1990 to 2010. *Global Heart* 9: 171-180, 2014.

84. **Sawyer BJ, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, and Gaesser GA**. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. *Journal of applied physiology (Bethesda, Md : 1985)* 121: 279-288, 2016.

85. **Schreuder TH, Green DJ, Hopman MT, and Thijssen DH**. Acute impact of retrograde shear rate on brachial and superficial femoral artery flow-mediated dilation in humans. *Physiological reports* 2: e00193, 2014.

86. **Shenouda N, Gillen JB, Gibala MJ, and MacDonald MJ**. Changes in brachial artery endothelial function and resting diameter with moderate-intensity continuous but not sprint interval training in sedentary men. *Journal of applied physiology (Bethesda, Md : 1985)* jap.00058.02017, 2017.

87. **Siasos G, Mourouzis K, Oikonomou E, Tsalamandris S, Tsigkou V, Vlasis K, Vavuranakis M, Zografos T, Dimitropoulos S, Papaioannou TG, Kalampogias A, Stefanadis C, Papavassiliou AG, and Tousoulis D**. The role of endothelial dysfunction in aortic aneurysms. *Current pharmaceutical design* 21: 4016-4034, 2015.

88. **Silvestro A, Scopacasa F, Oliva G, de Cristofaro T, Iuliano L, and Brevetti G**. Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. *Atherosclerosis* 165: 277-283, 2002.

89. **Soden PA, Zettervall SL, Ultee KH, Darling JD, Buck DB, Hile CN, Hamdan AD, and Schermerhorn ML**. Outcomes for symptomatic abdominal aortic aneurysms in the

826 American College of Surgeons National Surgical Quality Improvement Program. *Journal of*
827 *vascular surgery* 2016.
828 90. **Storen O, Helgerud J, Saebo M, Stoa EM, Bratland-Sanda S, Unhjem RJ, Hoff J,**
829 **and Wang E**. The Impact of Age on the VO2max Response to High-Intensity Interval Training.
830 *Med Sci Sports Exerc* 2016.
831 91. **Suh GY, Les AS, Tenforde AS, Shadden SC, Spilker RL, Yeung JJ, Cheng CP,**
832 **Herfkens RJ, Dalman RL, and Taylor CA**. Hemodynamic changes quantified in abdominal
833 aortic aneurysms with increasing exercise intensity using mr exercise imaging and image-based
834 computational fluid dynamics. *Annals of biomedical engineering* 39: 2186-2202, 2011.
835 92. **Sui X, LaMonte MJ, Laditka JN, Hardin JW, Chase N, Hooker SP, and Blair SN**.
836 Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *JAMA : the journal*
837 *of the American Medical Association* 298: 2507-2516, 2007.
838 93. **Sung S-H, Wu T-C, Chen J-S, Chen Y-H, Huang P-H, Lin S-J, Shih C-C, and Chen**
839 **J-W**. Reduced number and impaired function of circulating endothelial progenitor cells in
840 patients with abdominal aortic aneurysm. *Int J of Cardiol* 168: 1070-1077, 2013.
841 94. **Sung SH, Wu TC, Chen JS, Chen YH, Huang PH, Lin SJ, Shih CC, and Chen JW**.
842 Reduced number and impaired function of circulating endothelial progenitor cells in patients
843 with abdominal aortic aneurysm. *Int J Cardiol* 168: 1070-1077, 2013.
844 95. **Tew GA, Moss J, Crank H, Mitchell PA, and Nawaz S**. Endurance exercise training in
845 patients with small abdominal aortic aneurysm: a randomized controlled pilot study. *Archives of*
846 *physical medicine and rehabilitation* 93: 2148-2153, 2012.
847 96. **Tew GA, Weston M, Kothmann E, Batterham AM, Gray J, Kerr K, Martin D,**
848 **Nawaz S, Yates D, and Danjoux G**. High-intensity interval exercise training before abdominal
849 aortic aneurysm repair (HIT-AAA): protocol for a randomised controlled feasibility trial. *BMJ*
850 *open* 4: e004094, 2014.
851 97. **Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, Parker B,**
852 **Widlansky ME, Tschakovsky ME, and Green DJ**. Assessment of flow-mediated dilation in
853 humans: a methodological and physiological guideline. *American journal of physiology Heart*
854 *and circulatory physiology* 300: H2-12, 2011.
855 98. **Thijssen DH, Bullens LM, van Bemmel MM, Dawson EA, Hopkins N, Tinken TM,**
856 **Black MA, Hopman MT, Cable NT, and Green DJ**. Does arterial shear explain the magnitude
857 of flow-mediated dilation?: a comparison between young and older humans. *American journal of*
858 *physiology Heart and circulatory physiology* 296: H57-64, 2009.
859 99. **Thijssen DH, Carter SE, and Green DJ**. Arterial structure and function in vascular
860 ageing: are you as old as your arteries? *J Physiol* 594: 2275-2284, 2016.
861 100. **Thijssen DH, Dawson EA, Black MA, Hopman MT, Cable NT, and Green DJ**.
862 Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci*
863 *Sports Exerc* 41: 1072-1079, 2009.
864 101. **Thijssen DH, Dawson EA, Tinken TM, Cable NT, and Green DJ**. Retrograde flow
865 and shear rate acutely impair endothelial function in humans. *Hypertension* 53: 986-992, 2009.
866 102. **Thijssen DH, Schreuder TH, Newcomer SW, Laughlin MH, Hopman MT, and**
867 **Green DJ**. Impact of 2-Weeks Continuous Increase in Retrograde Shear Stress on Brachial
868 Artery Vasomotor Function in Young and Older Men. *Journal of the American Heart*
869 *Association* 4: 2015.

103. **Tinken TM, Thijssen DH, Hopkins N, Black MA, Dawson EA, Minson CT, Newcomer SC, Laughlin MH, Cable NT, and Green DJ**. Impact of shear rate modulation on vascular function in humans. *Hypertension* 54: 278-285, 2009.
104. **Tjonna AE, Rognmo O, Bye A, Stolen TO, and Wisloff U**. Time course of endothelial adaptation after acute and chronic exercise in patients with metabolic syndrome. *J Strength Cond Res* 25: 2552-2558, 2011.
105. **Trial TUSA**. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 352: 1649-1655, 1999.
106. **Verhoeven EL, Kapma MR, Groen H, Tielliu IF, Zeebregts CJ, Bekkema F, and van den Dungen JJ**. Mortality of ruptured abdominal aortic aneurysm treated with open or endovascular repair. *Journal of vascular surgery* 48: 1396-1400, 2008.
107. **Waeckel L, Badier-Commander C, Damery T, Kohler R, Sansilvestri-Morel P, Simonet S, Vayssettes-Courchay C, Wulff H, and Feletou M**. Vascular dysfunctions in the isolated aorta of double-transgenic hypertensive mice developing aortic aneurysm. *Pflugers Archiv : European journal of physiology* 467: 1945-1963, 2015.
108. **Walsh JH, Bilsborough W, Maiorana A, Best M, O'Driscoll GJ, Taylor RR, and Green DJ**. Exercise training improves conduit vessel function in patients with coronary artery disease. *Journal of applied physiology (Bethesda, Md : 1985)* 95: 20-25, 2003.
109. **Weston M, Batterham AM, Tew GA, Kothmann E, Kerr K, Nawaz S, Yates D, and Danjoux G**. Patients awaiting surgical repair for large abdominal aortic aneurysms - Can exercise at moderate to hard intensities with a low risk of adverse events. *Frontiers in physiology* 7: 684, 2016.
110. **Wnuk BR, Durmala J, Ziaja K, Kotyla P, Wozniewski M, and Blaszczak E**. A Controlled Trial of the Efficacy of a Training Walking Program in Patients Recovering from Abdominal Aortic Aneurysm Surgery. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University* 25: 1241-1371, 2016.
111. **Woodman RJ, Playford DA, Watts GF, Cheetham C, Reed C, Taylor RR, Puddey IB, Beilin LJ, Burke V, Mori TA, and Green D**. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. *Journal of Applied Physiology* 91: 929-937, 2001.
112. **Wray DW, Witman MA, Ives SJ, McDaniel J, Trinity JD, Conklin JD, Supiano MA, and Richardson RS**. Does brachial artery flow-mediated vasodilation provide a bioassay for NO? *Hypertension* 62: 345-351, 2013.
113. **Yang Z, Wang JM, Chen L, Luo CF, Tang AL, and Tao J**. Acute exercise-induced nitric oxide production contributes to upregulation of circulating endothelial progenitor cells in healthy subjects. *J Hum Hypertens* 21: 452-460, 2007.
114. **Yoo JK, Pinto MM, Kim HK, Hwang CL, Lim J, Handberg EM, and Christou DD**. Sex impacts the flow-mediated dilation response to acute aerobic exercise in older adults. *Experimental gerontology* 91: 57-63, 2017.

Table Legend

Table 1. Characteristics of patients with AAA and healthy adults

Data are displayed as mean±SD or number (%). BMI, body mass index; AAA, abdominal aortic aneurysm; MI, myocardial infarction; CABG, coronary artery bypass graft; ARB, Angiotensin II receptor blockers; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$, oxygen uptake; RER, respiratory exchange ratio.

Table 2. Flow-mediated dilation and hemodynamic indices at rest and following acute exercise in healthy adults and patients with AAA

Data are displayed as mean±SD. Absolute FMD (mm) was not logged for analysis. For conventional presentation of FMD%, absolute FMD data was logged for LMM analysis, back-transformed and interpreted as % change. For clarity, post-hoc p values are reported in the text only. For FMD% significant group ($p=0.044$), time ($p<0.001$), and intensity effects ($p<0.001$), and an intensity x time interaction ($p<0.001$) were observed. There were no group x time ($p=0.154$) or group x intensity x time ($p=0.697$) interactions. *significantly different to baseline $^{\#}$significantly different to seated rest (control condition) $^{\alpha}$significantly different between moderate- and high-intensity exercise. FMD, flow-mediated dilation; SRauc, shear rate area-under-the-curve; TTP, time to peak diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Figure Legend

Figure 1. Study protocol for patients with AAA and healthy adults.

Rest, supine position; FMD, flow-mediated dilation; Condition, control (no exercise seated rest), moderate-intensity continuous cycling (40% peak power-output), higher-intensity interval cycling (12x1 min at 70% peak power-output, separated by 1 min 10% peak power-output); Rest/Recovery, supine position

Figure 2. Relationship between $\dot{V}O_{2peak}$ (ml.kg^{-1}.min^{-1}) and basal flow-mediated dilation including both abdominal aortic aneurysm patients (squares) and healthy older adults (triangles).

Figure 3. Mean (black circles) and individual (lines) ΔFMD (%) from baseline at 10 and 60 min after control, moderate- and higher-intensity exercise in healthy adults (left panels) and patients with AAA (right panels).

Data are displayed as mean±95% CI. Significant intensity effect ($p<0.001$), time effect ($p=0.028$), intensity x time interaction ($p=0.033$). No group effect ($p=0.128$), or group x intensity x time interaction ($p=0.522$). *significantly different to baseline $^{\#}$significantly different to moderate-intensity exercise $^{\neq}$significantly different to control $^{\beta}$significantly different to 10-min post. AAA, abdominal aortic aneurysm; FMD, flow-mediated dilation.

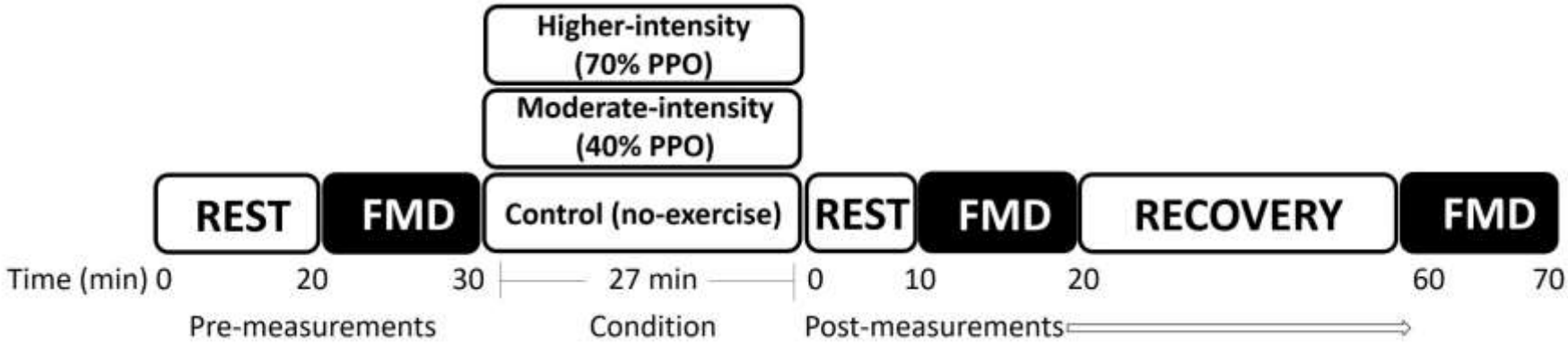
Higher-intensity
(70% PPO)
Moderate-intensity
(40% PPO)
REST
FMD
Control (no-exercise)
REST
FMD
RECOVERY
FMD
Time (min) 0
20
30
27 min
0
10
20
60
70
Pre-measurements
Condition
Post-measurements

Figure 1.

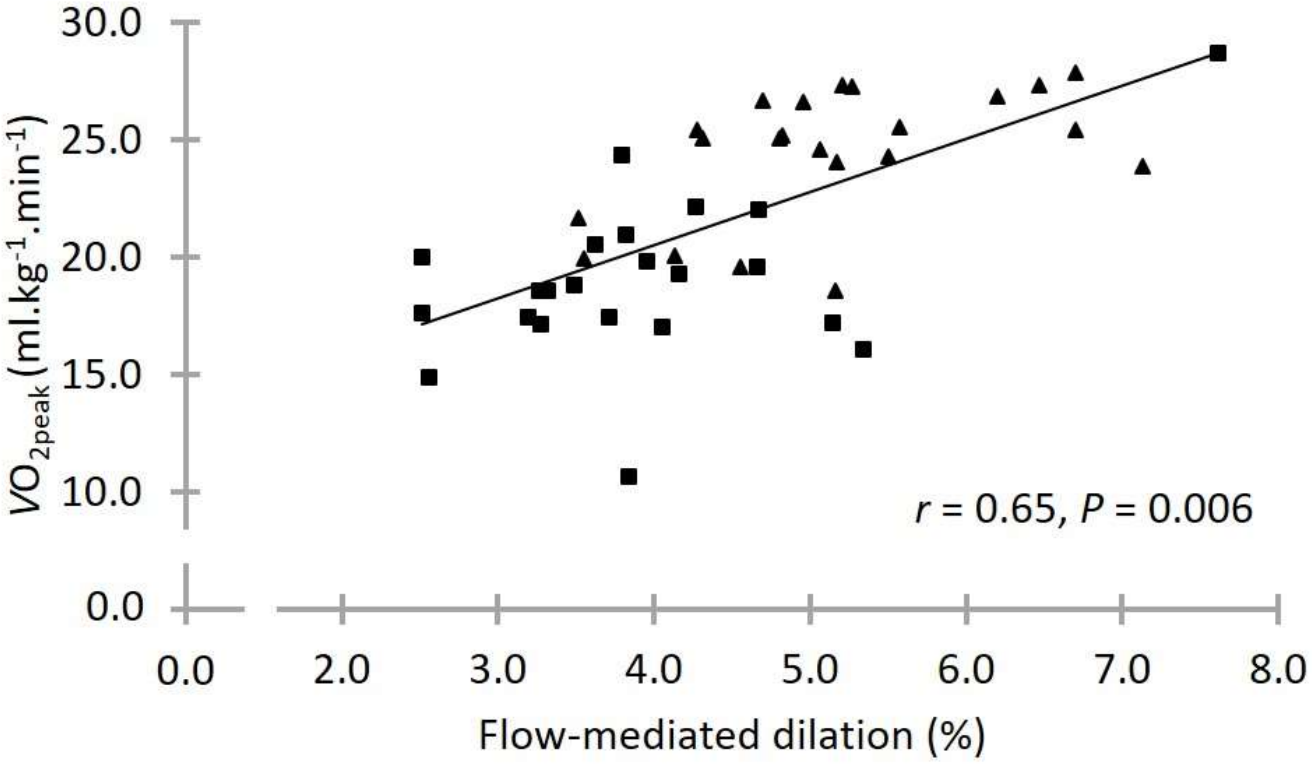
30.0
25.0
20.0
15.0
10.0
0.0
VO_{2peak} (ml.kg^{-1}.min^{-1})
r = 0.65, P = 0.006
0.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Flow-mediated dilation (%)

Figure 2.

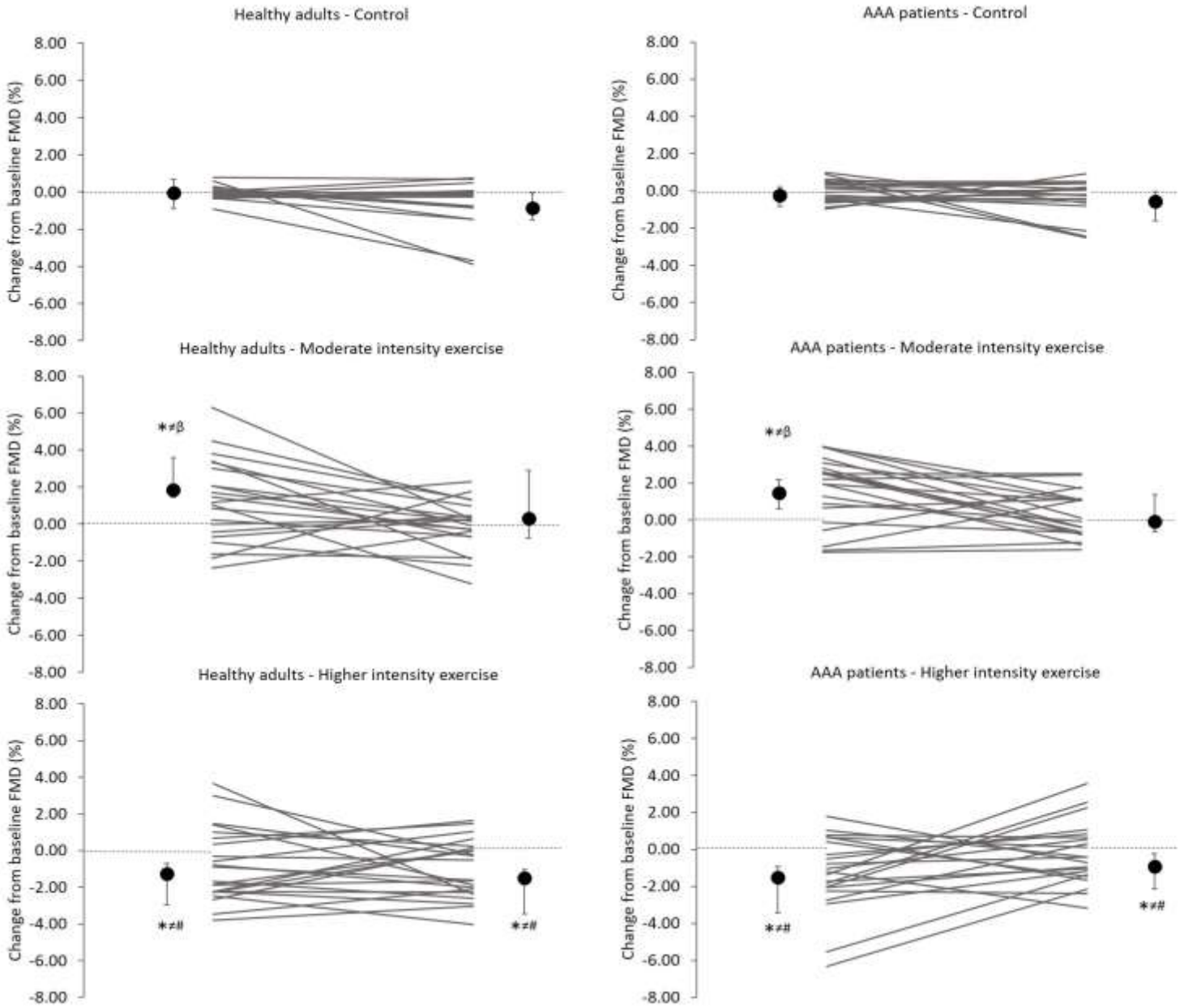
Healthy adults - Control
AAA patients - Control
Healthy adults - Moderate intensity exercise
AAA patients - Moderate intensity exercise
Healthy adults - Higher intensity exercise
AAA patients - Higher intensity exercise
Change from baseline FMD (%)
Chnage from baseline FMD (%)
8.00
6.00
4.00
2.00
0.00
-2.00
-4.00
-6.00
-8.00
*≠β
*≠#

Table 1.	**AAA patients (*n*=22)**	**Healthy adults (*n*=22)**	***P* value**
Age, years	74±6	72±6	0.200
Male, %	100	100	-
Height, m	1.73±0.07	1.75±0.07	0.463
Weight, kg	83.8±15.7	79.1±11.3	0.264
BMI, $kg.m^{-2}$	27.9±3.9	26.1±3.5	0.100
Clinical information			
Maximum AAA diameter (mm)	36±5	-	-
Hypertension, N (%)	15 (68)	5 (22)	0.006
Dyslipidaemia, N (%)	18 (82)	8 (36)	0.005
Diabetes	2 (9)	0 (0)	0.478
Smoking, current N (%)	2 (9)	1 (5)	0.697
Smoking, previous N (%)	12 (55)	11 (50)	0.701
Previous stroke, N (%)	2 (9)	0 (0)	0.488
Previous MI, N (%)	6 (27)	1 (5)	0.021
Previous CABG, N (%)	11 (50)	1 (5)	0.002
Medication			
ARB/ACE inhibitors, N (%)	9 (40)	4 (18)	0.140
Anti-platelet, N (%)	13 (60)	2 (9)	0.003
Beta-blockers, N (%)	9 (40)	2 (9)	0.034
Calcium channel blockers, N (%)	4 (18)	1 (5)	0.345
Statins, N (%)	20 (90)	9 (40)	0.001
Hemodynamic variables			
Resting heart rate, bpm	59±8	57±8	0.354
Brachial SBP, mmHg	129±13	124±11	0.206
Brachial DBP, mmHg	73±7	73±9	0.970
Peak Cardiorespiratory fitness			
Absolute VO_2, $L.min^{-1}$	1.58±0.36	1.94±0.35	0.002
Relative VO_2, $mL.kg^{-1}.min^{-1}$	19.03±3.54	24.47±2.78	<0.001
Peak heart rate, bpm	126±15	148±16	<0.001
Age-predicted peak heart rate, %	86±10	97±11	<0.001
Peak RER, AU	1.17±0.10	1.19±0.11	0.575
Peak Power, Watts	120±20	150±30	<0.001

Table 2

	Control (No Exercise)			Moderate-intensity continuous exercise			Higher-intensity interval exercise		
	Baseline	**Post, 10 min**	**Post, 60 min**	**Baseline**	**Post, 10 min**	**Post, 60 min**	**Baseline**	**Post, 10 min**	**Post, 60 min**
Flow-mediated dilation				***Healthy adults***					
Artery diameter, mm	4.75±0.50	4.67±0.56	4.63±0.53*	4.78±0.56	4.74±0.54$^{\#}$	4.75±0.52	4.85±0.50	4.90±0.53*$^{\#\,\alpha}$	4.87±0.55
FMD, mm	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01	0.03±0.01*$^{\#\alpha}$	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01
Rest blood flow, mL.s^{-1}	1.25±0.70	1.12±0.54	0.98±0.67*	1.34±0.61	1.69±1.02*$^{\#}$	0.97±0.67*	1.44±0.68	2.16±1.43*$^{\#}$	0.99±0.56*
Peak blood flow, mL.s^{-1}	5.25±1.95	4.88±2.36	4.23±2.36*	4.92±2.14	5.42±2.14*$^{\#}$	5.03±2.70	5.28±3.02	6.45±2.46*$^{\#\,\alpha}$	5.35±2.84$^{\#}$
SR_{AUC}, 10^3 s^{-1}	14.03±5.42	13.85±8.58	13.37±7.31*	14.32±8.38	16.90±8.22*$^{\#}$	13.98±7.84	16.20±7.32	17.55±7.94*$^{\#\,\alpha}$	14.61±6.50*
TTP diameter, *s*	64±23	58±24	70±31	62±31	66±25	63±30	65±32	69±28	63±22$^{\#}$
FMD, %	5.06±1.50	5.12±1.10	4.75±1.10	5.20±1.58	6.14±1.94*$^{\#\,\alpha}$	5.30±1.30	4.96±1.09	3.84±1.95*$^{\#\,\alpha}$	4.00±1.43*$^{\,\alpha}$
Heart rate and blood pressure									
Heart rate, bpm	59±10	56±9	54±7	58±8	71±15*$^{\#}$	59±9	58±7	68±10*	58±6
Systolic BP, mmHg	123±15	130±15*	128±15*	126±13	132±13*	127±15	123±11	130±13*	123±11
Diastolic BP, mmHg	72±10	76±10	74±10	74.10±	76±8	75±11	73±9	76±9	75±10
MAP, mmHg	87±11	91±11*	90±11*	89±10	93±9*	86±10	87±9	92±11*	88±9
Flow-mediated dilation				***Abdominal aortic aneurysm patients***					
Artery diameter, mm	4.90±0.38	4.90±0.40	4.80±0.44*	4.81±0.52	4.77±0.53$^{\#}$	4.76±0.54	4.94±0.50	4.95±0.46	4.93±0.43
FMD, mm	0.02±0.01	0.02±0.01	0.02±0.01	0.02±0.01	0.03±0.01*$^{\#\,\alpha}$	0.02±0.01	0.02±0.01	0.01±0.01*	0.02±0.01
Rest blood flow, mL.s^{-1}	1.14±0.78	0.85±0.57	0.60±0.47*	0.95±0.60	1.44±1.01*$^{\#\,\alpha}$	0.88±0.92	1.10±0.63	1.69±1.38*	1.14±0.85$^{\#}$
Peak blood flow, mL.s^{-1}	4.28±1.89	3.78±1.49	2.76±1.36*	3.77±1.74	4.89±2.26*$^{\#}$	4.19±1.78$^{\#}$	3.94±1.92	4.73±1.57*	4.45±2.23$^{\#}$
SR_{AUC}, 10^3 s^{-1}	10.26±6.17	9.33±5.50	7.26±3.89*	9.83±5.70	12.46±7.58*$^{\#}$	10.72±6.77$^{\#}$	9.86±5.90	13.50±5.95*	11.01±4.35*
TTP diameter, *s*	56±29	53±23	54±26	55±31	56±26	61±24	59±36	70±27*$^{\,\alpha}$	56±28
FMD, %	3.94±1.29	4.01±1.51	3.73±1.71	3.73±1.06	4.97±1.49*$^{\#}$	4.28±1.69	4.02±1.39	3.00±1.39*$^{\,\alpha}$	3.91±1.67*$^{\,\alpha}$
Heart rate and blood pressure									
Heart rate, bpm	59±9	56±8	56±10	60±9	68±11*$^{\#}$	58±8	59±9	69±11*$^{\#}$	60±8
Systolic BP, mmHg	127±11	136±14*	135±18*	130±15	133±16*	130±15	129±15	133±14*	127±13
Diastolic BP, mmHg	72±6	76±7	75±9	74±9	74±8	73±8	73±8	69±8	73±8
MAP, mmHg	88±7	93±9*	94±12*	90±9	92±9*	89±10	89±9	90±10*	89±9